Q & A

Lily Jan

Lily Jan is Jack and DeLoris Lange Professor of Physiology and Biophysics at the University of California, San Francisco (UCSF) and an investigator of the Howard Hughes Medical Institute. She began her long-term collaboration with her husband Yuh Nung Jan when they both took the neurobiology summer courses at Cold Spring Harbor (CSH) right after they finished graduate school at Caltech in 1974; they started recordings from the Drosophila *larval neuromuscular junction during the last few days of the CSH lab course and went on to identify Shaker as a behavioral mutant with defective potassium channel function while they were postdocs in Seymour Benzer's lab at Caltech. Their subsequent collaboration as postdocs in Steve Kuffler's lab at Harvard led to the identification of a peptide transmitter that generates the late slow excitatory postsynaptic potential (EPSP) in neurons that have no synaptic contact with the peptide-releasing nerve terminals, thereby providing evidence for 'action at a distance' of peptide transmitters that can diffuse and excite neurons tens of microns away. Because Yuh Nung and Lily Jan both believed in the importance of molecular identification of the ion channel of interest so that each channel type can be studied one at a time, ion channel studies in their lab at UCSF began with molecular identification of the founding members of three channel families, starting with Shaker cloning for voltage-gated potassium channels in 1987 and followed with expression cloning of the IRK1 inwardly rectifying potassium channel in 1993 and the TMEM16A calcium-activated chloride channel (CaCC) in 2008. These ion channel studies encompass biophysical queries about how a channel works, cell biological questions about how the channel number as well as channel properties may be regulated to modulate channel activity, and physiological analyses of channel function in neurons and other cell types.*

How did you become a biologist? After graduating from the National Taiwan University with a bachelor's degree in physics in 1968, I went to Caltech to study theoretical high-energy physics with George Zweig as my thesis advisor. After a couple years in the physics graduate program Yuh Nung and I both switched to biology under the influence of Max Delbrück. The trials and tribulations of my early years as a total novice trying to figure out whether I could do experiments in biology — too long a story to be told here that involves among other things thousands of chicken heads and an intimidating rabbit — are included in an autobiographical chapter Yuh Nung Jan and I wrote for the eighth volume of the *History of Neuroscience in Autobiography*, edited by Larry Squire. This volume will be published this year, and will join the archival chapters available online (http://www.sfn.org/about/history-of-neuroscience/autobiographical-chapters) in due course.

I have fond memories of catching up with George Zweig during our induction to the National Academy of Sciences in 1997. To biologists, George is known for his second major scientific contributions — in neurobiology — after his first major contribution proposing that mesons and other strongly interacting particles are composed of subatomic particles that George named aces while he was working at CERN in Geneva in 1964 (these subatomic particles were independently proposed by Murray Gell-Mann, also in 1964, and dubbed with the name quarks, their more commonly known name). In 1971 George turned his attention from physics to sound transduction in the cochlea. His profound understanding of the way the human inner ear responds to sound led to his design of a music synthesizer for part of the sound track for the Star Trek movie, and other novel devices for speech analyses. So here we have the happy circumstance that my physics professor and I the pupil both became biologists in the seventies.

And what drew you to your specific field of research? Yuh Nung and I began our collaboration after graduate school with a simple idea that genetic studies could help to identify critical molecules and pathways in neurobiology. In addition to the ion channel studies that began with screening *Drosophila* behavioral mutants via electrophysiological recording while we were in Benzer's lab at Caltech, which were resumed in our lab at UCSF with *Shaker* cloning, we initiated another collaboration after we joined the UCSF faculty in 1979, again starting with genetic studies in *Drosophila* but this time for the purpose of identifying genes and pathways that are important

for neurodevelopment, including those that control neuronal cell fate specification, asymmetric cell division, and more recently, dendrite development.

The ion channel studies and neurodevelopment studies in our lab have begun to intersect in interesting ways. Questions about how a neuron could modify specific synapses on its dendrites based on the activity at individual synapses have drawn us to study how local translation of ion channels in dendrites may be regulated by synaptic activity. And questions about what neuronal function befits a particular form of dendrites have led us to study mechanosensitive ion channels. The combination of *Drosophila* genetics with electrophysiology and behavioral studies offers the hope for molecular identification of mechanosensitive channels with specific physiological functions.

How do you balance work and family? We drove with our baby daughter across the country to Boston, and then again in the other direction to San Francisco when she was a toddler. Her younger brother was born a few years after we set up our lab at UCSF. We decided early on that it is important to have at least one parent around — whereas it works to some extent to schedule meetings with students and postdocs, only by being there could we provide the stability and capture the moments when our children have something to say or ask — and for that reason we refrained from traveling at the same time. That was how we settled into the routine that I would attend ion channel meetings while Yuh Nung would attend development meetings. It has turned out to be a good arrangement for me to work closely with our channel group and for Yuh Nung to work closely with the development group, so each of us would have one-on-one discussions with lab members and can count on the other with the broad perspective of the forest rather than the up-close view of the trees.

As I've said to students and postdocs over the years, evolution has bestowed us with the capacity to manage raising children on top of other things we need to do. It is a lot of work but then it is truly rewarding to have this bond with our offspring from an impressionable young age to adulthood.

Who were your key early influences? Max Delbrück provided the initial spark by asking a biologist to give a talk in the Caltech physics seminar series with the blatant intent to recruit physicists into the field of biology (as relayed by the speaker at the outset of his seminar, Max wanted the hearts and souls rather than just the hands and minds of physicist converts). As his graduate student, I was exposed to a wide range of topics that were of interest to Max in his journal clubs and courses, including Bernard Katz's book "*Nerve, Muscle, and Synapse*" and Clay Armstrong's preprints about potassium channel gating deduced from channel block by tetraethylammonium (TEA) and related compounds. I recall Max making the unusual move of going to a national meeting so he could gather opinions about the prospect of purifying potassium channels (the prospect was deemed dim). Fortunately, as it turns out it is possible to get around this obstacle via positional cloning of *Shaker* associated with altered potassium channel functions, thanks to the *Drosophila* polytene chromosomes.

Seymour Benzer provided the example of assembling a group of spirited bright students and postdocs and leaving them with free reign to choose their research topics. We have learned a great deal from Seymour and our peers in his lab, and cherish our long-lasting friendship with them. This style of running the lab is one we like and could emulate. Nowadays, for incoming lab members I would first tell them what's going on in the lab and then let the newcomers tell me what they like to pursue after they've had the chance to talk with current lab members. My job is to provide them with support based on what I know and what I can glean from the literature, while leaving them with ample room for exploration. For postdocs ready to start their own labs we believe it is important for them to be able to continue with the projects they've worked on in our lab, not only to facilitate their grant applications but also to allow them to hit the ground running. We have kept up with many of our lab alumni and maintained a list of their current position and contact info on our lab website (http://physio.ucsf.edu/jan/FormerPersonnel.html). It has been gratifying and fun to see so many of our lab alumni flourishing and often establishing rewarding collaborations with one another.

What do you think are the big questions to be answered next in your field? How does an ion channel work? How do channels mediate or influence cellular functions such as neuronal signaling? These very basic questions remain at the forefront of the channel field. Is this an indication of slow progress? Not at all, but since these questions can be pursued more readily once the molecular identity is established for a channel, we are just beginning to address those questions for channels that have recently emerged with newly acquired molecular identity even though their physiological importance and therapeutic values may have been well known for decades.

For channels with either newly acquired or long established molecular identity, the depth and scope of scientific inquiries depend very much on the experimental repertoire available. Throughout the years we have benefited from the development of various new technologies driven by a desire to better understand the function and regulation of ion channels. The ingenuity and innovation in and beyond the channel field will likely determine which big questions will be answered next.

What's that mountain trail behind you in the photo, and is that a bird to your left? Inca trail. And yes, Yuh Nung captured the image of that bird soaring by Wayna Picchu (the mountain next to Machu Picchu). Now that our daughter is getting her MFA (master for arts) this year and our son with a PhD in cancer biology is finishing medical school next year for the physician scientist track, we've got an empty nest and have traveled together from time to time. Last year we had the nice opportunity for some hiking in Peru after we both attended the Argentina neuroscience meeting.

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